

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PAC23-WO01	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, Item 5 below.	
International application No. PCT/GB2004/001559	International filing date (day/month/year) 08/04/2004	(Earliest) Priority Date (day/month/year) 16/04/2003
Applicant CELLTECH R&D LIMITED		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐

The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (See Box II).

3. ☐ Unity of invention is lacking (see Box III).

4. With regard to the title,☒

the text is approved as submitted by the applicant.

☐

the text has been established by this Authority to read as follows:

5. With regard to the abstract,☐

the text is approved as submitted by the applicant.

☒

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regards to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. _____

☐

as suggested by the applicant.

☐

as selected by this Authority, because the applicant failed to suggest a figure.

☐

as selected by this Authority, because this figure better characterizes the invention.

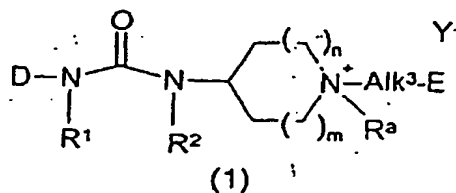
- b. ☐ none of the figures is to be published with the abstract.

International application No.

PCT/GB2004/001559

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

Compounds of formula (I)



wherein, m, n, R¹, R², R³, ALK³, E and Y:

are as defined in the claims, being potest and selective inhibitors of chemokine binding to the CXCR3 receptor, are accordingly of use in the treatment and/or prevention of conditions involving inappropriate T-cell trafficking, including inflammatory, autoimmune and immunoregulatory disorders such as rheumatoid arthritis.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2004/001559

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D211/58 C07D409/12 A61K31/452 A61P37/02 A61P37/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, EMBASE, BIOSIS, MEDLINE, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/16353 A (DRAFFAN ALISTAIR GEORGE ; MELLOR SARAH LOUISE (GB); BATTY DUNCAN (GB);) 28 February 2002 (2002-02-28) cited in the application claims 1,14,16,17; example 46	1-11
Y	WO 00/76512 A (OATES BRYAN ; CHAPMAN KEVIN T (US); FINKE PAUL E (US); MACCOSS MALCOLM) 21 December 2000 (2000-12-21) cited in the application claims 1,17-19,21,22	1-11
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

21 July 2004

Date of mailing of the international search report

04/08/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

vanVoorst tot Voorst, M

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2004/001559

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NAYA A ET AL: "DESIGN, SYNTHESIS, AND DISCOVERY OF A NOVEL CCR1 ANTAGONIST" 2001, JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, PAGE(S) 1429-1435 , XP002946303 ISSN: 0022-2623 the whole document	1-11
P,Y	WO 03/104198 A (SATO MASAKAZU ; MATSUNAGA YUKO (JP); TAKAYAMA TETSUO (JP); UMEMIYA HIR) 18 December 2003 (2003-12-18) examples, claim 1	1-11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB2004/001559

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0216353	A	28-02-2002	AU 7995801 A	04-03-2002
			EP 1311502 A1	21-05-2003
			WO 0216353 A1	28-02-2002
			US 2003171413 A1	11-09-2003
WO 0076512	A	21-12-2000	AU 5473400 A	02-01-2001
			WO 0076512 A1	21-12-2000
			US 6500844 B1	31-12-2002
WO 03104198	A	18-12-2003	WO 03104198 A1	18-12-2003

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/GB2004/001559

International filing date (day/month/year)
08.04.2004

Priority date (day/month/year)
16.04.2003

International Patent Classification (IPC) or both national classification and IPC
C07D211/58, C07D409/12, A61K31/452, A61P37/02, A61P37/08

Applicant
CELLTECH R&D LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80293 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

vanVoorst tot Voorst, M

Telephone No. +49 89 2399-8280



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY****Box No. I Basis of the opinion**

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☐ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2004/001559

Box No. II Priority

1. ☒ The following document has not been furnished:

☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-11
	No: Claims	

Inventive step (IS)	Yes: Claims	
	No: Claims	1-11

Industrial applicability (IA)	Yes: Claims	1-11
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and /or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

AD SECTION V:

1. The following documents are considered:

D1: WO 02/16353 A (DRAFFAN ALISTAIR GEORGE ; MELLOR SARAH LOUISE (GB); BATTY DUNCAN (GB);) 28 February 2002 (2002-02-28)
D2: WO 00/76512 A (OATES BRYAN ; CHAPMAN KEVIN T (US); FINKE PAUL E (US); MACCOSS MALCOLM) 21 December 2000 (2000-12-21)
D3: NAYA A ET AL: "DESIGN, SYNTHESIS, AND DISCOVERY OF A NOVEL CCR1 ANTAGONIST" 2001, JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, PAGE(S) 1429-1435 , XP002946303 ISSN: 0022-2623

The priority documents pertaining to the present application were not available at the time of establishing this written opinion. Hence, it is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the document WO 03/104198 A (SATO MASAKAZU ; MATSUNAGA YUKO (JP); TAKAYAMA TETSUO (JP); UMEMIYA HIR) 18 December 2003 (2003-12-18) cited in the International Search Report could become relevant to assess whether claims 1-11 satisfy the criteria set forth in Article 33(1) PCT.

2. The compounds disclosed in D1 differ from those of the application in that they are acetamide-derivatives, D2 does not disclose piperidinium derivatives as considered in the present application and the D3-compounds differ in the D-NR¹-group from the compounds claimed.

Having regard to the prior art cited in the International Search Report the subject-matter claimed appears to meet the requirements of Article 33(2) PCT.

3. Closest prior art comprises the compounds disclosed in D1-D3, which possess similar pharmacological activities, i.e. they are useful in the treatment of inflammatory, autoimmune and immunoregulatory disorders.
The problem to be solved was to provide compounds that are potent and selective modulators of the interaction between CXCR3 and its chemokine ligands.
Having regard to the structurally closely related prior art cited, it would appear, that the skilled person faced with the above problem would have expected such an activity from the present compounds.

Whether or not the structural modifications of the state of the art are associated

with an improvement at all is a fundamental aspect of inventive step. Unless evidence refutes the assumption that the small modifications made are not unexpectedly associated with a significant improvement in the property relevant to the solution of the stated problem, the presumption prevails that the compounds represent only predictable effects and are therefore obvious. The solution of the problem of merely providing further compounds showing the above mentioned activities does not involve an inventive step.

Thus in the absence of any unexpected effect or advantage of the compounds claimed an inventive step as required by article 33(3) PCT cannot be acknowledged. The Applicant is requested to demonstrate, preferably by means of comparative tests, whereon an inventive step could be based.

4. No objections with regard to Article 33(4) PCT arise for claims 1-11.

AD POINT VI:

Certain documents cited

Certain published documents

<u>Application No</u> <u>Patent No</u>	<u>Publication date</u> <u>(day/month/year)</u>	<u>Filing date</u> <u>(day/month/year)</u>	<u>Priority date (valid claim)</u> <u>(day/month/year)</u>
WO03/104198	18.12.2003	10.06.2003	11.06.2002

From the INTERNATIONAL BUREAU

HK

PCT

SECOND AND SUPPLEMENTARY NOTICE
INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION (TO DESIGNATED OFFICES
WHICH APPLY THE 30 MONTH TIME
LIMIT UNDER ARTICLE 22)

(PCT Rule 47.1(c))

To:

THOMPSON, John
Celltech R & D Limited
Patents Department
208 Bath Road
Slough
Berkshire SL1 3WE
ROYAUME-UNI

Date of mailing (day/month/year)
18 August 2005 (18.08.2005)

23 AUG 2005

PATENTS DEPT

Applicant's or agent's file reference
PAC23-WO01

IMPORTANT NOTICE

International application No.
PCT/GB2004/001559

International filing date (day/month/year)
08 April 2004 (08.04.2004)

Priority date (day/month/year)
16 April 2003 (16.04.2003)

Applicant

CELLTECH R & D LIMITED et al

- ATTENTION:** For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), does not apply, please see Form PCT/IB/308(First Notice) issued previously.
- Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, does apply, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93bis.1. The International Bureau has effected that communication on the date indicated below:
04 November 2004 (04.11.2004)

AU, AZ, BY, CN, CO, DZ, EP, HU, KG, KP, KR, MD, MK, MZ, NA, RU, SY, TM, US

In accordance with Rule 47.1(c-bis)(i), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

- The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, does apply, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93bis.1:

AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BW, BZ, CA, CR, CU, CZ, DE, DK, DM, EA, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, JP, KE, KZ, LC, LK, LR, LS, LT, LV, MA, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PG, PH, PL, PT, RO, SC, SD, SG, SK, SL, TJ, TN, TR, TT, UA, UZ, VC, VN, YU, ZA, ZW

In accordance with Rule 47.1(c-bis)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

4. TIME LIMITS for entry into the national phase

For the designated or elected Office(s) listed above, the applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain of the designated or elected Office(s) listed above. For regular updates on the applicable time limits (30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pc/en/index.html>.

It is the applicant's sole responsibility to monitor all these time limits.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Nora Lindner

Facsimile No.+41 22 740 14 35

Facsimile No.+41 22 338 89 65

INTERNATIONAL SEARCH REPORT

PCT/GB2004/001559

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D211/58 C07D409/12 A61K31/452 A61P37/02 A61P37/08		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D A61K A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, EMBASE, BIOSIS, MEDLINE, BEILSTEIN Data, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/16353 A (DRAFFAN ALISTAIR GEORGE ; MELLOR SARAH LOUISE (GB); BATTY DUNCAN (GB);) 28 February 2002 (2002-02-28) cited in the application claims 1,14,16,17; example 46	1-11
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-/--		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *Z* document member of the same patent family		
Date of the actual completion of the international search 21 July 2004		Date of mailing of the international search report 04/08/2004
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016		Authorized officer vanVoorsttotVoorst, M

INTERNATIONAL SEARCH REPORT

PCT/GB2004/001559

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NAYA A ET AL: "DESIGN, SYNTHESIS, AND DISCOVERY OF A NOVEL CCR1 ANTAGONIST" 2001, JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, PAGE(S) 1429-1435 , XP002946303 ISSN: 0022-2623 the whole document	1-11
P,Y	WO 03/104198 A (SATO MASAKAZU ; MATSUNAGA YUKO (JP); TAKAYAMA TETSUO (JP); UMEMIYA HIR) 18 December 2003 (2003-12-18) examples, claim 1	1-11

INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/GB2004/001559

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 0216353	A	28-02-2002	AU	7995801 A		04-03-2002
			EP	1311502 A1		21-05-2003
			WO	0216353 A1		28-02-2002
			US	2003171413 A1		11-09-2003
WO 0076512	A	21-12-2000	AU	5473400 A		02-01-2001
			WO	0076512 A1		21-12-2000
			US	6500844 B1		31-12-2002
WO 03104198	A	18-12-2003	WO	03104198 A1		18-12-2003